REMARKS

The Office Action mailed July 16, 2004, for the present application has been reviewed. The present amendment replaces all pending claims with new claims numbered 79-88 drawn to "vaccine compositions." Considered together with the following remarks, these changes are believed sufficient to place the application into condition for allowance.

No new matter has been added to the application. Support for reworded claims is found throughout the specification, in particular at page 3, lines 2-10; page 3, lines 14-16; page 3, lines 28-36; page 4, lines 19-26; page 11, lines 14-20; page 11, lines 21-25; page 15, lines 1-7; page 15, lines 8-11; page 15, lines 16-19; page 18, lines 4-11; page 19, line 15 to page 20, line 6; page 22, lines 29-35; page 23, lines 16-18; page 28, lines 18-21; page 29, lines 1-13; page 35, line 20 to page 39, line 10; page 39, lines 13-25; page 40, lines 24-31; page 47, lines 4-17.

Applicants express appreciation for thoughtful examination by the Examiner.

Elections/Restrictions.

The Examiner previously imposed a restriction requirement, identifying 19 separately patentable claimed inventions. Additionally, the Examiner required an election of species within identified restriction groups. See Office Action of October 2, 2003. Applicants elected group I, claims drawn to polypeptides and immunogenic fragments. Claims were reworded to be generic such that no election of "species" was made between full length 30 kD polypeptide and its immunogenic. See response dated April 2, 2004. The Present Action sustains this restriction (election of species)

requirement in its entirety. Claims drawn to immunogenic fragments have been withdrawn from consideration as "non-elected species."

Applicants respectfully request reconsideration of this restriction requirement with respect to election of species within elected group I. See Office Action of October 2, 2003, at ¶ 13. Specifically, Applicants request withdrawal of the requirement that an election be made between full length polypeptide and immuno-crossreactive (epitopic) fragments of full length polypeptide. As currently worded, all claims are drawn to vaccine compositions comprising HP30 polypeptides. Applicants submit that epitopic fragments of full length HP30 polypeptides are obvious in light of Applicants' disclosure of the full length amino acid sequence and its use in therapeutic vaccine compositions. Election of species should not be required where the claimed species are obvious over each other. See MPEP 808.01(a).

In light of Applicants' disclosure, those skilled in the art would be motivated to identify epitopic fragments of HP30, a known therapeutic, immunoprotective *Helicobacter* antigen. As of the time of filing of this application, December 7, 2000, techniques of "epitope mapping" were routine experimentation in the art. It was well known that antibodies recognize epitopes of approximately 6 amino acid residues (Davies et al. 1996. Interactions of protein antigens with antibodies. Proc Natl Acad Sci USA 93(1):7-12). It was well known that, with respect to T-cell epitopes, immune responses are generated against immunogenic proteins by "processing" in antigen presenting cells – that is by degradation of full length immunogenic polypeptides into epitopic fragments (Janeway et al. 1990. Immunogenicity; proceedings of UCLA Symposium held at Steamboat Springs, Colorado, January 21-28, 1989. Alan R. Liss,

Inc. New York, NY; Roitt et al. 1989. Immunology, 2nd Edition. Gower Medical Publishing, London England). It was well known that T-cell epitopes are linear, or continuous amino acid sequences, and that comparatively small fragments could define dominant or minor T-cell epitopes (Janeway et al. 1990. Immunogenicity; proceedings of UCLA Symposium held at Steamboat Springs, Colorado, January 21-28, 1989. Alan R. Liss, Inc. New York, NY; Roitt et al. 1989. Immunology, 2nd Edition. Gower Medical Publishing, London England). It was well known in the art that B-cell epitopes could be formed either by a continuous amino acid sequence or could be conformational, that is, formed by a discontinuous set of residues from different portions of the overall amino acid sequence (Janeway et al. 1990. Immunogenicity; proceedings of UCLA Symposium held at Steamboat Springs, Colorado, January 21-28, 1989. Alan R. Liss, Inc. New York, NY; Roitt et al. 1989. Immunology, 2nd Edition. Gower Medical Publishing, London England). Even discontinuous, conformational epitopes could be readily identified by protocols of "epitope mapping" known in the art. An entire volume of Epitope Mapping Protocols had been published by the end of 1996 (Morris (editor). 1996. Epitope Mapping Protocols. Humana Press, Totwa, N.J.). Applicants thus respectfully submit that, given the disclosed full length HP30 coding and translated sequences (SEQ ID NO: 3 and SEQ ID NO: 4), those skilled in the art have a reasonable expectation of success in determining epitopic fragments using these well known, widely used, routine techniques.

Claim Objections

The Present Action objects to all pending claims as drawn to non-elected embodiments of the invention. The Action further objects to claims involving vaccine adjuvants identified as "QS21, MF59, CPG, PML and PLG." Applicants respectfully submit that the objection is obviated by the present amendments to the claims.

Claim rejections under 35 U.S.C. § 102(b)

The Action rejects claims drawn to HP30 polypeptides as anticipated by the genome of *H. pylori* strain 26695 published by J. Tomb et al. in "The complete genome sequence of the gastric pathogen *Helicobacter pylori*," Nature (1997), 388:539. The Action states: "Tomb et al. disclose an isolated Helicobacter polypeptide, designated HP1588 ... wherein the polypeptide was expressed recombinantly and ...shares 100% sequence identity with SEQ ID NO: 4."

In response, Applicants respectfully note that the Action appears to err in concluding that Tomb et al. disclose any "recombinantly expressed" polypeptides. Tomb et al. neither recombinantly expressed nor isolated any polypeptide nor even any specific nucleic acid. Tomb et al. sequenced the genome of *H. pylori* strain 26695. In so doing, Tomb et al. identified 1590 predicted genes, that is, hypothetical ORFs. These are proteins that might or might not actually be expressed *in vivo*. Applicants acknowledge that one of 1590 hypothetical ORFs predicted by Tomb et. al., identified as translated sequence HP1588, does have 100% identity with SEQ ID NO:4. However, this disclosure by Tomb et al. does not anticipate claims to isolated polypeptides comprising SEQ ID NO:4, much less claims as currently drawn to

vaccine compositions comprising such polypeptides. Tomb et al. clearly identify HP1588 as a "hypothetical protein." See Table 2, appendix. Tomb et al. did not express or isolate HP1588. Indeed, nothing in Tomb et al. teaches or suggests that HP1588 should be isolated or even demonstrates that HP1588 actually exists *in vivo*.

Applicants respectfully request the rejection be withdrawn with respect to Tomb et al. (1997). To qualify as prior art under 35 U.S.C. 102(b), a reference must teach each and every element of a claim. See MPEP 2131 citing *Verdegaal Brothers v Union Oil Co. of California*, 814 F. 2d 628, 631 (Fed. Cir. 1987). Tomb et al. do not teach use of HP1588 as a vaccine composition.

The Present Action additionally rejects claims drawn to both HP30 polypeptides and "immunogenic compositions" comprising such polypeptides as anticipated by the disclosure of Smith et. al. in "Nucleic acid and amino acid sequences relating to *Helicobacter pylori* for diagnostics and therapeutics," WO 96/40893. The Action states: "WO96/40893 discloses an isolated Helicobacter polypeptide...wherein the polypeptide was expressed recombinantly, and is an HP30 polypeptide that shares identity with SEQ ID NO: 4...WO96' also discloses a method of stimulating an immune response to the H. pylori polypeptides."

In response, first, Applicants respectfully note that the Action appears to err in concluding that Smith et al. disclose an isolated, recombinantly expressed polypeptide that shares identity with SEQ ID NO:4. Applicants acknowledge that one of the more than 900 hypothetical ORFs disclosed by Smith et al., identified as coding sequence "12ge20305orf30," does have 97% identity with the HP30 coding sequence disclosed here as SEQ ID NO:3. See Exhibit A [BLAST 2 SEQUENCES alignment is shown for

HP30 coding sequence SEQ ID NO: 3, top, and 12ge20305orf30, disclosed by Smith et al., bottom]. Smith et al. do not, however, disclose any isolated polypeptide corresponding to a translation product of coding sequence 12ge20305orf30. Smith et al. identify 12ge20305orf30 as coding sequence SEQ ID NO: 1279 and as translated sequence SEQ ID NO: 1730. See Table 1, section B.11, "other cytoplasmic proteins," at page 41. Smith et al. actually expressed and isolated only 10 recombinant polypeptides, corresponding to translation products of only 10 of the more than 900 hypothetical ORFs disclosed. None of these 10 polypeptides was coded by SEQ ID NO: 1279 or had amino acid sequence corresponding to SEQ ID NO: 1730. That is, none of these 10 polypeptides "shares identity with SEQ ID NO: 4." See Table 5, page 100-101 and see page 102 line 23 to page 103, line 11.

Second, Applicants submit Smith et al. cannot anticipate the present invention, drawn to "vaccine compositions," because Smith et al. did not enable a vaccine composition that "shares identity" with HP30. It is well settled that prior art under 35 U.S.C. § 102(b) must teach and enable each element of the claimed invention. See e.g. *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985)["[E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling."].

Douglas Smith, the first-named inventor of WO 96/40893, is himself co-author of a publication that discloses the genome of *H. pylori* strain J99. See Alm et al. 1999, Genomic-sequence comparison of two unrelated isolates of the human gastric pathogen *Helicobacter pylori,* Nature 397:176, Reference AP in Applicants' Second Supplemental Information Disclosure Statement filed September 10, 2002.

WO 96/40893 is based almost entirely on this published *H. pylori* J99 genome sequence. The disclosure of WO 96/40893 is almost entirely bio-informatic. Claims are drawn to each of more than 900 hypothetical ORFs predicted from the J99 genome sequence. Smith et al. seek to claim each of these hypothetical gene products not only as "purified polypeptides" but also as "vaccines." See claims 56, 61, 72, 73, 81, 87, 93 and 99.

Applicants respectfully submit that Smith et al. have not enabled each of their more than 900 "vaccine composition" claims. Only 10 of more than 900 hypothetical polypeptides were actually expressed and "purified," having been identified as "vaccine candidates" based on homologies to known proteins and based on predicted exposure to extracellular contact. See page 102, lines 23-28 and see Table 5, page 100. Moreover, of these ten "vaccine candidates," only nine were actually tested, and only 3 actually demonstrated a significant immunoprotective effect. See Fig. 3 and Fig. 4 and page 105, lines 1-28. Smith et al. clearly identify 12ge20305orf30, the translation product of which "shares identity with SEQ ID NO: 4," as a cytoplasmic protein – not obviously a "vaccine candidate." See Table 1, section B.11, at page 41. Indeed, the only suggestion by Smith et al. that this hypothetical polypeptide would make a useful vaccine composition was their *claim* for this and 366 other hypothetical, cytoplasmic protein "vaccines." See claims 87 and 61.

Applicants respectfully submit that the "vaccine" claiming by Smith et al. in WO 96/40893 is analogous to "mere naming" of chemical compounds. It is well established that, to enable, a disclosure must provide guidance sufficient to provide those skilled in the art with a working invention, without need for "undue

experimentation." The amount of guidance required is inversely proportional to predictability of the art. In a highly unpredictable field such as the vaccine art, considerable guidance is required. See MPEP 2164.01 and see MPEP 2164.03. Applicants respectfully submit that, where only 1 in 3 of the very best "vaccine candidates" identified by the latest bio-informatic approaches actually worked, those of ordinary skill in the art could not, without "undue experimentation," identify which of the more than 900 less desirable, hypothetical polypeptide "vaccines" disclosed by Smith et al. actually worked. Accordingly, Smith et al. cannot be said to have enabled their claim to a vaccine comprising a polypeptide that "shares identity with SEQ ID NO: 4."

Applicants respectfully request the rejection be withdrawn with respect to Smith et al. (1999).

Claim rejections under 35 U.S.C. § 103(a)

The Action rejects claims to "immunogenic compositions" comprising HP30 polypeptides as obvious in light of Tomb et al. (1997) and WO 96/40893 (1999).

In response, first, Applicants respectfully note that claims as amended are drawn to "vaccine compositions," not merely "immunogenic compositions."

Second, Applicants respectfully submit that no *prima facie* case of obviousness of HP30 "vaccine compositions" can be established based on Tomb et al. (1997) and WO 96/40893 (1999). *Prima facie* obviousness requires that references suggest the invention and also that those skilled in the art have a "reasonable expectation of success" in making and using it. See MPEP 2142. As explained above, nothing in Tomb et al. teaches or suggests that HP1588 should be isolated, much less used in a

vaccine, or demonstrates that HP1588 actually exists *in vivo*. As explained above, the only suggestion by Smith et al. that the translation product of 12ge20305orf30 should be used as a vaccine is their *claim* for this and 366 other hypothetical, cytoplasmic protein "vaccines." See claims 87 and 61. Those skilled in the art would have no "reasonable expectation of success" using any one of the more than 900 "vaccines" disclosed by Smith et al. Accordingly, the present claims to "vaccine compositions" are not obvious in light of Tomb et al. (1997) and WO 96/40893 (1999).

Applicants respectfully request the rejection be withdrawn.

CONCLUSION

In light of the foregoing, Applicants respectfully submit that they have addressed each and every item presented by the Examiner in this Office Action. Favorable reconsideration of all of the claims as amended is earnestly solicited. Applicants submit that the present application, with 10 pending claims, is in a condition for allowance and respectfully request such allowance.

In the event any further matters requiring attention are noted by Examiner or in the event that prosecution of this application can otherwise be advanced thereby, a telephone call to Applicants' undersigned representative at the number shown below is invited.

Respectfully submitted,

Date: January 12, 2005

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